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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/658,688	HERMANSON, GARY G.	
	Examiner	Art Unit	
	Anoop Singh	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *215, 216, 219, 221-232, 235, 237-246, 249, 251-262, 265,267-276, 279, 281-296* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *215,216,219,221-232,235,237-246,249,251-262,265,267-276,279 and 281-296* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendments to the claims and supplemental response filed on July 27, 2007has been received and entered. Claims 215, 231, 245, 261 and 265 have been amended, while claims 1-214, 217-218, 220, 233-234, 236, 247-248, 250, 263-264, 266 have been canceled. It is noted that applicants have also added claims 293-296.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/27/07 has been entered.

Election/Restrictions

Applicant's election with traverse of the invention of claims 174 and 214 (group II) filed January 30, 2006 was acknowledged. The traversal was on the grounds(s) that Examiner did not set forth convincing argument that the search and examination of group I along with elected group necessarily represents an undue burden for the examiner. Applicants' argument of examining plurality of polynucleotide composition with the elected group comprising a method of treating anthrax was found not persuasive. Applicant's argument of examining other sequences with elected Seq ID 4 was found not persuasive. Examiner also indicated that fragments and variants of SEQ ID NO: 4 such as SEQ ID 2, 6 and 8 would be examined as long as they depend on elected claims.

Claims 215, 216, 219, 221-232, 235, 237-246, 249, 251-262, 265,267-276, 279, 281-296 are under consideration.

New-Claim Rejections-Necessitated by the Amendments - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 215, 216, 219, 221-232, 235, 237-246, 249, 251-262, 265,267-276, 279, 281-296 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method to reduce the severity of anthrax infection in a vertebrate comprising: administering to a vertebrate in need thereof a composition comprising a carrier, (+)-N- (3-aminopropyl)-N,N-dimethyl-2,3-bis(syn-9-tetradecenyloxy)-l-propanaminium bromide (GAP-DMORIE) or DMRIE, a co-lipid selected from the list consisting of 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE), 1,2-diphytanoyl-sn-glycero-3-phosphoethanolamine (DPyPE), and 1,2-dimyristoyl-glycer-3-phosphoethanolamine(DMPE) and an isolated polynucleotide comprising a nucleic acid fragment which encodes a polypeptide at least 97% identical to amino acids 30 to 764 of SEQ ID NO:4, wherein the amino acid of said polypeptide corresponding to amino acid Ser-Arg-Lys-Lys-Arg-Ser at position 192 to 197 of SEQ ID NO: 4 have been deleted; wherein said composition elicits an immune response to said polypeptide; and wherein said nucleic acid fragment is a variant fragment of an optimized coding region for the polypeptide of SEQ ID NO: 4 as set forth in claim 215; wherein said vertebrate generates an effective immune response thereby reducing the severity of anthrax infection; does not reasonably provide enablement for a method of prophylactic vaccination to prevent or protect against anthrax infection. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by applicant would not have had to perform

"undue experimentation" to make and/or use the invention claimed. Such a determination is not a simple factual consideration, but is a conclusion reached by weighing at least eight factors as set forth in In re Wands, 858 F.2d at 737, 8 USPQ 1400, 2d at 1404. Such factors are: (1) The breadth of the claims; (2) The nature of the invention; (3) The state of the art; (4) The level of one of ordinary skill in the art; (5) The level of predictability in the art; (6) The amount of direction and guidance provided by Applicant; (7) The existence of working examples; and (8) The quantity of experimentation needed to make and/or use the invention.

The office has analyzed the specification in direct accordance to the factors outlines in *In re Wands*. MPEP 2164.04 states: "[W]hile the analysis and conclusion of a lack of enablement are based on factors discussed in MPEP 2164.01(a) and the evidence as whole, it is not necessary to discuss each factor in written enablement rejection." These factors will be analyzed, in turn, to demonstrate that one of ordinary skill in the art would have had to perform "undue experimentation" to make and/or use the invention and therefore, applicant's claims are not enabled.

Claims 215 and 245 are drawn to a method to prophylactically vaccinate a vertebrate against anthrax infection comprising administering to a vertebrate in need thereof a composition comprising a carrier and a nucleic acid fragment that encodes a polypeptide at least 97% identical to amino acid 30 to 764 of SEQ ID NO: 4 which are variants of an optimized coding region for the polypeptide of SEQ ID NO: 4 for eliciting an efective immune response to said polypeptide resulting in prevention or reduction in severity of anthrax infection. In addition, it is noted that claims 231and 261 are directed to a method of treating anthrax infection by delivering the composition of the invention. It is emphasized although claims 276, 279, 281-292 are drawn to a composition and carrier, however they are also analyzed for their intended use in method of preventing and reducing the severity of anthrax infection anthrax infection as contemplated in the instant invention.

The aspects considered broad are: methods of prophylactically vaccinate a vertebrate against anthrax infection by eliciting a prophylactic effective immune response thereby protecting said vertebrate against anthrax infection.

It is noted that as recited, claimed invention reads on broad genera of DNA vaccine by delivering codon-optimized polynucleotide to elicit immune response. The specification fails to provide an enabling disclosure for the claimed invention because the specification fails to provide sufficient guidance as to (i) how an artisan of skill would have practiced the claimed method in preventing any form of anthrax infection by administering of codon optimized polynucleotide, (ii) the claimed method would have resulted in immune response sufficient to prevent any form of anthrax. An artisan would have to carry out extensive experimentation to make and use the invention, and such experimentation would have been undue because art of DNA vaccine in general in humans is unpredictable and specification fails to provide specific guidance to practice the invention over full scope. As will be shown below, these broad aspects were not enabled for the claimed invention at the time of filing of this application because neither the specification nor the art of record taught sufficient guidance to practice the invention over full scope of the claims. For purposes to be shown in the state of the prior art, the question of lack of enablement is discussed.

The specification provides a general description of anthrax infection and describes the role of toxins consisting of gene product protective antigen, lethal factor, and edema factor in the virulence of *Bacillus anthracia* infection (pp 1-2). The specification also describe the need for optimization of coding regions encoding polypeptides from pathogen codon frequencies preferred in a mammalian species resulting in enhanced expression in the cells of that mammalian species and concomitant increase in immunogenicity (pp 5). The invention is directed to enhance immune response of a vertebrate that require protection against anthrax by administering in vivo a polynucleotide comprising a codon optimized coding region encoding a component of *Bacillus anthracia* lethal toxin (pp 5-6). Pages 7-11 describe brief description of the drawing. Pages 11-67 of the specification provides a detailed description of the invention, preferred embodiments and provide definition of terms, codon optimization (pp 21-54), methods and administration of claimed compositions of the invention (pp 54). Rest of the specification provides specific examples of plasmid vectors, compositions and experimental details (pp 68-120).

While the specification provides a description of DNA vaccine for the protection and treatment against anthrax infection, specification does not enable administering DNA vaccine to prophylactically vaccinate a vertebrate against anthrax infection to generate prophylactically effective immune response thereby protecting said vertebrate against anthrax infection. While progress has been made in recent years in development of DNA vaccine against viral as well as bacterial infection, however, desired immune response for sustained period to prophylactically vaccinate to prevent disease such as anthrax remains unpredictable and inefficient in humans.

The state of the post filing art effectively summarized by the references of Galloway et al (Expert Opin Biol Ther. 2004, 4(10): 1661-7, IDS) describe progress made in DNA vaccine for the treatment and prevention against anthrax infection. Galloway state, " a number of factors may account for poor immunogenicity of plasmid DNA in non human primate and human. Of the prime importance is the issue of DNA uptake and antigen presentation" (pp 1665, col. 1, last para). It is disclosed that codon usage and cationic lipids improve the efficacy of the antigen presentation and resulting immune response. However, Galloway concludes, " the field of DNA vaccination remains largely an experimental and some what empirical science" (pp 1665, col. 2, para. 4, lines 1-4). They highlight some advantages of using DNA vaccine but also acknowledge the fact the no DNA vaccine is yet produced is not the research failure but rather realization of complex role of immune system (pp 1665, col. 2, para. 4). The prior art of record on treating anthrax by recombinant anthrax vaccine was unpredictable as a number of question remain unanswered that require experiment that are not routine to determine whether the vaccine would be efficacious in any patient.

Given this lack of reasonable predictability in Applicant's specification and the art, the Artisan would require a large amount of information from Applicant's examples to provide the guidance to provide reasonable predictability.

Applicant's examples describe the construction of an isolated polynucleotide comprising a human codon optimized PA, LF, fragments and variants thereof encoding full length *B. Anthracis* protective antigen (PA), LF and variant. The results show *in vitro* expression of human codon optimized coding regions encoding *B. Anthracis* PA, LF and

fragments in a murine and human cell lines. It is noted that the samples were assayed by western blot and ELISA using anti PA, anti LF antibodies (pp 88-89). Examples 8 and discloses mouse, rabbit, non-human primate and human immunization by administering plasmid constructs intramuscularly and immunological assay to determine LF and PA antibody titer (pp 93-95). Examples 11-12 describe immunization of mice and rabbit using codon optimized *B. Anthracis* DNA vaccine in different cationic lipid formulations. The results show higher neutralizing antibody titer. The example also teaches immunization of rabbit using codon optimized intramuscular administration of *B. Anthracis* DNA vaccine followed by aerosol administration of 50-250 LD_{50} equivalent of *B. Anthracis* (Ames strain) spores. The results show that all the codon optimized DNA vaccine formulations had comparable efficacy as compared to commercially available AVA vaccine. Examples 14-15 describe immunization of mice using formulation that is prepared by adding sterile plasmid DNA and sterile DMRIE: DOPE SUV liposome in a final molar ratio of 4:1 or 2:1 plasmid DNA to DMRIE and non human primate immunized by VR6292 formulation with Vaxfectin. The data shows enhanced anti PA IgG titer in different formulations (table 19-23). Example 16 shows long-term immune response in DNA immunized rabbit after anthrax spore challenge (pp 112, table 24).

Although instant application shows the potential role of codon optimized DNA vaccine against *B. Anthracis* infection, however, the specification does not provide any evidence that codon optimized polynucleotide could be delivered to confer immunity resulting in protection against any anthrax infection commensurate with full scope of the claims in any vertebrate. For instance, den Hurk et al (Immunol Rev. 2004; 199:113-25) emphasizes that the concept of DNA immunization has proven to be extremely successful in inducing immune responses in mice; however, significant barriers exist to effective induction of immunity in large animals and humans using DNA immunization. den Hurk et al states "Indeed, there is not one DNA vaccine that has been approved for either human or veterinary use. This lack is mainly due to their relatively low efficacy, specifically in target species (emphasis added) (see page 114, col. 1, last para.). den Hurk et al also desribes that chemokines have also been incorporated into DNA vaccines for mice, these compounds have not been reported in target speestablishes

any nexus between the effect seen in mice extrapolated to human. In fact, most of the prior and post filing art teach difficulty in achieving effective induction of immunity in large animals and humans as supported by the art of record (supra). It is noted that den Hurk while describing the role of adjuvants in DVA vaccination states variable immune rsponse in different species depnding on route and site of adminstration. den Hurk descibes "plasmid encoding gB and gD from PRV that are administered intramuscularly together with various combinations of the cytokine constructs along with GM-CSF show enhanced immune response and protection against virus, while the IL-2 and IFN-γ constructs had no adjuvant effects". Contrary to this in an another study, co-administration of a plasmid encoding GM-CSF showed no significantly change the antibody or T-cell response in an immunized pigs (see page 116, col. 2). Furthermore, den Hurk,et al emphasize that the timing of delivery and the dose of the plasmid encoding the cytokine may be critical, and those issues have rarely been addressed (see page 119, col. 1, para 2). Thus, it is clear that a enhancement in immune response showed varying imuune response in different species with different adjuvant even after filing of instant application. The specification does not provide any specific guidance to indicate that administration of nucleic acid encoding the variants of optimized SEQ ID NO: 4 descibed in the specificaton would specifically show contemplate biological activity in humans. In adsence of evidence to the contrary, it is not clear that these elements may not be functional in human or in a comparable larger animal model in the same manner as they have been demonstrated in the mice or rabbit. Thus, the art of record at the time of the invention does not provide enabling support for the claimed invention to prophylactically vaccinate a vertebrate against anthrax infection. An artisan would have to perform undue experimentation to empirically test different composition, route and adjuvant formulation to determine if polynucleotide encoding polypeptide that has 97% similarity to SEQ ID NO:4 would elicit an immune response in human or any other comparable larger mammal as broadly recited in the instant claims. In the instant case, claims are directed to a method of prophylactically vaccinate any vertebrate against anthrax infection by administering a composition containing a nucleic acid encoding a protein. At the time of filing of this application, Rosenberg et al (Hum Gene

Ther. 2003 20; 14(8): 709-14) noted that contrary to effect seen in experimental animals, Rosenberg concludes that neither intramuscular nor intradermal injection of DNA encoding the gp100 nonmutated melanoma-melanocyte antigen was capable of raising cellular immune reactivity or a desired biological response in patients with metastatic melanoma (see page 713, co. 2, last para. and references of den Hurk, supra). The specification does not provide any specific guidance to overcome this art-recognized unpredictability that immune response seen in smaller experimental animal could be extrapolated to immune response at same levels in humans or other larger mammals. The art of record teaches difficultly in achieving any significant immune response in human upon administration of a plasmid or DNA vaccine. In the instant case, neither specification nor prior art provided adequate guidance to support that a method of generating effective immune response seen in mice or rabbit could be extrapolated to same level of antibody response in humans. Furthermore, while reviewing state of anthrax vaccine, Leppla et al (J Clin Invest. 2002,110(2): 141-4) raise a number of questions. Leppla et al describe that limited clinical data and substantial animal experimentation indicate that only a critical level of serum anti-PA antibodies confer immunity to both cutaneous and inhalation anthrax. Leppla further describe a number of other uncertainties including what would be the optimal concentration of serum antibodies in humans that confers immunity to anthrax. Thus, a regimen of dose scheduling as disclosed from small animal and primate would not be efficacious to confer immunity in humans. In addition, the level of antibody required to protect individual from the effects of a anthrax infection is uncertain, since this would be dependent upon how the infection is acquired (bio-terrorist attack, natural, Zoonotic) and the number of spores inhaled. Similarly, the efficacy of this DNA vaccine would also be different depending upon source and route of anthrax infection (inhalation, cutaneous). Leppla also questioned whether physicochemical and immunochemical assays could accurately predict the efficacy of a recombinant vaccine (pp 143, col. 2, para 2 bridging pp 144, col. 1, para. 1). The working example shows immune response against spore challenge of $50LD_{50}$- $250LD_{50}$. The specification exemplified "multiple dosing" of DNA vaccine composition at different time point (day 0, 28 and 56) resulting

in survival of rabbits challenged with anthrax for up to 3 weeks (see example 13 of the specification). However, these results are more consistent with the enabling scope of reducing the severity of anthrax infection resulting in prolonged survival of rabbit. These experiments do not provide evidence of protection against anthrax infection. Furthermore, none of the claims require multiple dosing of the claimed composition. It is emphasized that instant specification exemplified generating immune response in a controlled environment in mice and rabbit, however, neither specification nor prior art provide any specific guidance to extrapolate this data to generate prophylactic effective antibody in larger mammal or in humans against any dose of anthrax infection resulting in protection against anthrax infection. In view of foregoing the scope of instant claims go beyond those disclosed in the specification. Given the lack of guidance provided by the specification, one of skill in the art would be left to speculate as to the conditions and/or steps necessary for eliciting an immune response at appropriate level for sustained period of time in larger mammals. It would have required undue experimentation for one of skill in the art to make and use the invention as claimed without a reasonable expectation of success. It is noted that the unpredictability of a particular art area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). It is also well established in case law that the specification must teach those of skill in the art how to make and how to use the invention as broadly claimed. In re Goodman, 29 USPQ2d at 2013 (Fed. Cir. 1994), citing In re Vaeck, 20 USPQ2d at 1445 (Fed. Cir. 1991). The guidance provided by the specification to fails overcome the art recognized unpredictability of DNA vaccine to elicit immune response in larger mammal for sustained period of time. It would require undue experimentation for an Artisan to make and "use" the claimed invention and/or working examples demonstrating the same, such invention as claimed by the applicant is not enabled commensurate with full scope of the claims

In conclusion, in view of breadth of the claims and absence of a specific showing by Applicant, in the way of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by Applicant is not enabled for the

claimed inventions commensurate with full scope. The specification and prior art do not teach a method of prophylactically vaccinate a vertebrate against anthrax infection to prevent against anthrax infection caused by any type or severity. An artisan of skill would have required undue experimentation to practice the method as claimed because the art of prophylactic DNA vaccination for the protecting against anthrax infection in general in vivo was unpredictable at the time of filing of this application as supported by the observations in the art record.

Response to the Arguments

Applicant arguments and evidence filed on 07/27/2006 have been fully considered are persuasive to the extent claims embrace administering DNA vaccine via any route to elicit immune response and composition using any co-lipid with GAP-DMORIE/DMRIE. The rejections pertaining to these issues are withdrawn. However, applicants augment of prophylactically vaccinating any vertebrate against any dose and form of anthrax infection is not enabling for the reasons discussed in 112 rejections in preceding section.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 215, 216, 219, 221-232, 235, 237-246, 249, 251-262, 265,267-276, 279, 281-296 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 215, 231, 245, 261 an 275 are vague and indefinite to the extent they recite "said polypeptide corresponding to amino acid s 192 to 197 of SEQ ID NO: 4

have been deleted". The term "corresponding to" is defined as having or participating in the same relationship (as kind, degree, position or function) especially with regard to the same or like wholes. In the instant case, it is unclear if fragment nucleic acid encoding polypeptide which is only 97% identical to SEQ ID NO: 4 correspond to which amino acids of 192 to 197 of SEQ ID NO: 4. Does 192-197 refers to the same or related amino acid? Recitation of a direct reference of association corresponding to amino acid Ser-Arg-Lys-Lys-Arg-Ser at position 192 to 197 of SEQ ID NO: 4 would obviate the basis of this rejection. Claims 216, 219, 221-230, 232, 235, 237-244, 246, 249, 251-260, 262, 265,267-274, 276, 279, 281-296 are directly or indirectly depend on independent claims. Appropriate correction is required.

Withdrawn- -Claim Rejections - 35 USC § 103

Claims 215-292 e rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al (US Patent Application no US 2004/0009945, dated 1/15/2004, effective filing date 7/10/1998); Nagata et al (Biochem Biophys Res Commun. 1999, 261(2): 445-51) and Hartikka et al (2001, Vaccine 19:1911-1923) is withdrawn in view of amendemnts to the independent claims now requieing deletion of amino aacid at position 192-197 of seq ID NO: 4. However, upon further consideration a new rejection is made in view of amendmenst to the claims.

New -Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 215-216, 219, 222-228, 231, 232, 235, 238-243, 275, 276, 279, 282-290 and 293are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al (US

Patent Application no US 2004/0009945, dated 1/15/2004, effective filing date 7/10/1998); Klimpel (Proc Natl Acad Sci U S A. 1992; 89(21): 10277-81), Singh et al (J Biol Chem. 1994; 269(46): 29039-46), Nagata et al (Biochem Biophys Res Commun. 1999, 261(2): 445-51) and Hartikka et al (2001, Vaccine 19:1911-1923, art of record).

Lee et al teach a method and composition for using the nontoxic protective antigen (PA) protein from *B. anthracis* in inducing an immune response that is protective against anthrax in subjects (abstract). It is noted that Lee et al disclose a SEQ ID NO: 6 (PA) that has 100% sequence similarity with claimed SEQ ID NO: 4 (see sequence search report). It further disclosed that nucleic acid molecules could encode portions or fragments of the nucleotide sequences and variants of disclosed sequence (pp 2, para. 24 and 25). Lee et al emphasize that it would be routine for one skilled in the art to generate the degenerate variants, for instance, to optimize codon expression for a particular host (pp 2, para. 21, col. 2, lines 1-5). It is noted that Lee et al exemplified a PA sequence wherein the secretory signal has been removed (MAT-PA) (SEQ ID NO:2), or replaced with other known secretory signals such as tissue plasminogen activator (TPA) secretory signal resulting in a DNA fragment encoding TPA-PA (SEQ ID NO:3). Furthermore, Lee et al also teach isolated nucleic acid that includes DNA molecules comprising a sequence substantially different from those described above but which, due to the degeneracy of the genetic code, still encode the *B. anthracis* proteins described and specified in SEQ ID NO:6 (PA) (see page 2, para. 21) that has ~100% sequence identity to SEQ ID NO: 4 of the instant application. In addition, Lee et al contemplate using pharmaceutical carrier to deliver disclosed nucleic acid composition for eliciting immune response in a subject via multiple route including intramuscular administration (see page 4, para 36). Since the disclosed nucleic acid sequence is from *B. anthracis*, the codon usage pattern is considered related with the translation efficiency of the gene in different organisms. It is also noted that these compositions were generally directed towards enhancing immunity against *B. anthracis.* The prior art differed from the claimed invention by not teaching a composition wherein amino acid 192-197 of SEQ ID NO; 4 is deleted and delivering a composition with

combination of lipids comprising polynucleotide encoding polypeptide of the invention that are codon optimized to enhance immune response in a subject.

However, prior to instant invention, Klimpel teaches Cleavage by a cellular protease at sequence, Arg-Lys-Lys-Arg, normally follows binding of Protective antigen (PA) to a cell surface receptor. . Using several mutant proteins Klimpel indicated that lethal factor-dependent toxicity required the sequence Arg-Xaa-Xaa-Arg. Klimpel demonstrated that mutant containing the sequence Ala-Lys-Lys-Arg was also toxic but required significantly more protein to produce equivalent toxicity (see abstract and Table 1, Figure 1). Klimpel conclude that furin is the cellular protease that activates PA, and that nearly all cell types contain at least a small amount of furin exposed on their cell surface (abstract). Likewise, Singh et al also disclose deletion of the 2 Phe rendered PA completely non-toxic. It is also noted that Singh cite Klimpel to describe that introduction of mutations at this site in combination with deletion of the activation site at residues 164-167 for furin cleavage site described by Klimpel produces an altered PA that may have several advantages for use in anthrax vaccines. Although, Klimpel and Singh both generally embraced the idea of introducing mutation in combination with deletion of activation of furin cleavage site but differed from claimed invention by not disclosing a vaccine composition against anthrax infection.

At the time of invention, Nagata et al teach that the codon optimization level of the genes correlate well with the translational efficiency in mammalian cells (see Table 1B and discussion). It is noted that the results of Nagata et al suggest that DNA immunization using the gene codon-optimized to mammals through the entire region is very effective (abstract). The teachings of Nagata et al suggest that the DNA sequence obtained by optimized codon usage of a host considerably increases both humoral and cellular immune responses (Figure 3 and discussion). Further, the teachings of Nagata et al indicate that synthetic human immunodeficiency virus type 1 gp120 sequence in which most wild-type codons were replaced with codons from highly expressed human genes (page 445, right column) is considerably increased in comparison to that of the respective wild-type sequence suggesting a direct correlation between expression levels of a protein obtained by codon optimization and the immune response. Although,

Nagata generally teach that codon frequency table could be used to increases both humoral and cellular immune responses, but Nagata et al do not explicitly teach codon optimization for a nucleotide composition for the treatment of *B. anthracis* infection.

However, at the time the claimed invention was made, use of cationic lipid to deliver compositions to elicit immune response was routine in the art. Prior to instant invention, Hartikka et al teach variety of techniques to enhance humoral immune responses against pDNA-encoded antigen including co-injection of pDNA with neutral, anionic and/or cationic lipids. It is noted that Hartikka et al tested many carrier for improving the immune response and also disclose the optimized cationic carrier lipid:colipid formulation (1:1 molar mixture) of the cationic lipid (±)-*N*-(3-aminopropyl)-*N*,*N*-dimethyl-2,3-*bis*(*cis*-9-tetradecenyloxy)-1-propanaminium bromide, and a commercial colipid di-(3,7,11,15-tetramethyl-hexadecanoyl)phosphatidyl-ethanolamine (see page 1920. col. 1, para. 1). Hartikka et al also emphasize the importance of using 1:1 molar ratio of this composition in order to achieve optimal immune response. Although Hartikka et al do not explicitly teach a method to treat or prevent anthrax infection he generally embraced the idea that cationic lipids could potentially be used as adjuvant in genetic vaccination.

Accordingly, in view of the teachings of Lee, Klimpel /Singh, Nagata and Hartikka, it would have been obvious for one of ordinary skill in the art, at the time the claimed invention was made, to modify the composition of Lee by optimizing the codons with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to make such a modification, as Lee had already disclosed that it would be routine for one skilled in the art to generate the degenerate variants, for instance, to optimize codon expression for a particular host (supra). Although Lee et al did not optimize the codon; he generally embraced potential of codon-optimized composition to reduce the severity of anthrax infection. In addition, Nagata also provided necessary guidance with respect to optimizing codon to improve immune response. In addition, one of ordinary skill in the art would have studied Klimpel/Singh and would have been further motivated to improve the composition of Lee by deleting the furin and or chymotrypsin or thermolysin cleavage site to further reduce the toxicity

associated withTPA-P63 sequence. Therefore, given that instant sequence and its potential to reduce the severity of anthrax were known in prior art as per the teachings of Lee, Klimpel/Singh, it would have been obvious for an artisan to deliver the composition comprising codon optimized polynucleotide encoding polypeptide and a carrier such as one disclosed by Hartikka. One of ordinary skill in the art would have used the carrier disclosed by Hartikka particularly since art provided reasoning that this optimized cationic carrier formulation would further enhance the immune response.

One who would practiced the invention would have had reasonable expectation of success because a composition comprising a polynucleotide disclosed by Lee that is modified to alter the bacterial codon usage to human codon usage and further modified as per the teaching of Klimpel/Singh to reduce the toxicity and delivered along with a carrier disclosed by Hartikka would have resulted in immune response to reduce the severity of anthrax infection. This would have allowed one of ordinary skill in art to combine the teaching of Lee, Klimpel/Singh, Nagata and Hartikka because a composition comprising codon optimized polynucleotide delivered along with a optimized cationic lipid would have resulted in an effective immune response to reduce the severity of anthrax infection.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

Claims 245-246, 249, 252-258, 261, 262, 265, 268-276, 279, 282-290, 295-296 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al (US Patent Application no US 2004/0009945, dated 1/15/2004, effective filing date 7/10/1998); Klimpel (Proc Natl Acad Sci U S A. 1992; 89(21): 10277-81), Singh et al (J Biol Chem. 1994; 269(46): 29039-46), Nagata et al (Biochem Biophys Res Commun. 1999, 261(2): 445-51) and San et al (Hum Gene Ther. 1993 Dec;4(6):781-8).

The combined teachings of Lee et al, Klimpel and Singh et al have been discussed above. However, none of the references explicitly teaches a carrier comprising DMRIE/DOPE.

However, prior to instant invention, it was routine to use plasmid DNA encoding the transgene complexed with a cationic lipid mixture, DMRIE/DOPE for in vivo DNA-based immunotherapy. Specifically, San et al teaches potential nonviral vectors for human gene therapy are DNA-liposome complexes. San et al disclose a novel cationic lipid, dimyristyloxypropyl-3-dimethyl-hydroxyethyl ammonium (DMRIE) that has been substituted into the DNA-liposome complex with dioleoyl phosphatidylethanolamine (DOPE), which both improves transfection efficiencies and allows increased doses of DNA to be delivered in vivo. San also reported that this improved cationic lipid formulation is well-tolerated in vivo and could therefore allow higher dose administration and potentially greater efficiency of gene transfer (see abstract). However, San differed form claimed invention by not disclosing a formulation of DMPRIE/DOPE complexed with DNA that would be effective against anthrax infection.

Accordingly, in view of the teachings of Lee, Klimpel /Singh, Nagata and San, it would have been obvious for one of ordinary skill in the art, at the time the claimed invention was made, to modify the composition of Lee by optimizing the codons with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to make such a modification, as Lee had already disclosed that it would be routine for one skilled in the art to generate the degenerate variants, for instance, to optimize codon expression for a particular host (supra). Although Lee et al did not optimize the codon; he generally embraced potential of codon-optimized composition to reduce the severity of anthrax infection. In addition, Nagata also provided necessary guidance with respect to optimizing codon to improve immune response. In addition, one of ordinary skill in the art would have studied Klimpel/Singh and would have been further motivated to improve the composition of Lee by deleting the furin and or chymotrypsin or thermolysin cleavage site to further reduce the toxicity associated withTPA-P63 sequence. Therefore, given that instant sequence and its potential to reduce the severity of anthrax were known in prior art as per the teachings of Lee, Klimpel/Singh, it would have been obvious for an artisan to deliver the composition comprising codon optimized polynucleotide encoding polypeptide and a carrier such as one disclosed by San with reasonable expectation of success. One of

ordinary skill in the art would have used the carrier disclosed by San particularly since art provided reasoning that this cationic carrier formulation would have enhanced the transfection efficiency and it was routine in art to use different lipid composition to enhance transfection efficiency.

One who would practiced the invention would have had reasonable expectation of success because a composition comprising a polynucleotide disclosed by Lee that is modified to alter the bacterial codon usage to human codon usage and further modified as per the teaching of Klimpel/Singh to reduce the toxicity and delivered along with a carrier disclosed by San would have resulted in immune response to reduce the severity of anthrax infection. This would have allowed one of ordinary skill in art would to combine the teaching of Lee, Klimpel/Singh, Nagata and San because a composition comprising codon optimized polynucleotide delivered along with a optimized cationic lipid would have resulted an effective immune response to reduce the severity of anthrax infection.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

Conclusion

No Claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anoop Singh whose telephone number is (571) 272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272- 4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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